

production of 5-(4-hydroxyphenyl)-5-phenylhydantoin.<sup>13</sup>

In order to obtain the desired 3'-bromo-4'-hydroxy derivative, 5-(4-hydroxyphenyl)-5-phenylhydantoin was dissolved in glacial acetic acid for bromination, or in cold 5% sodium hydroxide solution for iodination. Little difficulty was encountered in introducing two bromine or two iodine atoms, but no condition was discovered whereby only one atom of halogen was directly substituted into the phenylhydantoin. The 3'-bromo-4'-hydroxy compound was prepared by cleaving the methoxyl group in 5-(3-bromo-4-methoxyphenyl)-5-phenylhydantoin by refluxing with 48% hydrobromic acid solution; all attempts to prepare the mono-iodo analog were unsuccessful.

### Summary

1. This investigation includes the synthesis of seven examples of 5-phenyl-5-*m*-substituted

(13) A. F. Isbell, Ph. D. dissertation, University of Texas, 1943.

phenylhydantoin. These hydantoin are the first to be prepared from meta substituted benzophenones.

2. Four halogenated derivatives of *p*-aminobenzophenone and three halogenated derivatives of *p*-hydroxybenzophenone have been prepared; of these four have not previously been reported.

3. These halogenated derivatives of *p*-aminobenzophenone form hydantoin readily; to obtain the corresponding hydantoin derivatives of *p*-hydroxybenzophenone, it was necessary first to synthesize 5-(4-hydroxyphenyl)-5-phenylhydantoin and to subject the latter to bromination or iodination.

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## Synthesis of Aromatic Phosphonic Acids and Their Derivatives. I. The Derivatives of Benzene, Toluene and Chlorobenzenes

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The Michaelis<sup>1</sup> modification of the Friedel-Crafts reaction used for the preparation of aromatic dichlorophosphines from which a wide variety of aromatic derivatives of phosphorus can be obtained, gives very poor yields, usually below 20-25% and often below 10%. It has been seen readily that this is due to the loss, to all practical purposes, of the bulk of the chlorophosphines in the so-called complex layer during the extraction with petroleum ether. This layer of viscous matter comprises the complex between the aluminum chloride and the chlorophosphines and cannot be resolved into components by simple hydrolysis because of the formation of extremely stable aluminum salts of the resulting acids. The problem was thus seen to lie in a successful break-down of the complex, to be followed by the isolation of the phosphorus derivatives in a more manageable form than that presented by the chlorophosphines. Since trivalent phosphorus compounds react vigorously with halogens, such as chlorine, to form very stable halogen derivatives of pentavalent phosphorus, it was felt that halogenation, or specifically chlorination, of the reaction mixture would effect the desired break-down of the aluminum chloride complex. However, since the hydrolysis of such a mixture would still lead to the formation of stable and untractable aluminum salts, it was obviously necessary to convert the chlorophosphines into relatively stable derivatives before the removal from the reaction mixture of the undesired aluminum chloride by the most logical method, *i.e.*, by washing with water. The choice of the desirable derivative was made in favor of the esters, for reasons of economy and ease of handling. The application of the above principles

resulted in a significant improvement of the Michaelis reaction, which made it possible to effect the preparation of the esters of aromatic phosphonic acids in excellent yields, without the necessity of handling sensitive and malodorous intermediates. It was also found that the reaction can be made to yield compounds of the type  $R_2PO_2H$ , besides those of the type  $RPO_2H_2$ . This fact arises from the disproportionation of the initially-formed dichlorophosphines, which fact was observed by Michaelis as occurring on heating dichlorophosphines to high temperatures in sealed tubes. The presence of aluminum chloride apparently catalyzes this reaction and leads to the formation of di-substituted derivatives at ordinary reflux temperatures. The esters, isolated by distillation, can be readily converted into the corresponding acids by refluxing with concentrated hydrochloric acid, followed by evaporation in the cases of soluble types.

### Experimental

The general procedure used is given below. The hydrocarbon was mixed with the desired amounts of phosphorus trichloride and aluminum chloride and the mixture was refluxed, with protection against atmospheric moisture. The excess of phosphorus trichloride was then removed under reduced pressure, with stirring, at a temperature not in excess of 50-60°. The residual mass was diluted with one to two volumes of dry tetrachloroethane (other chlorinated solvents are somewhat less satisfactory) and was treated with dry chlorine, with good agitation and cooling by means of ice-water, until the absorption was complete; this generally required one to two hours for molar runs. An excess of alcohol (five moles per mole of the hydrocarbon) was then added slowly to the stirred and cooled mixture, with application of reduced pressure by means of a water pump to remove hydrogen chloride. The esterification is most satisfactorily conducted at about 15°. The reaction mixture was then treated with a mixture of ice and hydrochloric acid and the organic layer was

(1) Michaelis, *Ber.*, **12**, 1009 (1879).

TABLE I

RH	RP(O)(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>				R <sub>2</sub> P(O)OC <sub>2</sub> H <sub>5</sub>			
	°C.	B. p. Mm.	Found	Anal., % P Calcd.	°C.	B. p. Mm.	Found	Anal., % P Calcd.
Benzene	117-118	1.5	14.4	14.5	173-175	1.5	12.5	12.6
Chlorobenzene	117-119	1.5	12.5	12.45	182-183	1.5	9.85	9.85
<i>o</i> -Dichlorobenzene	155-157	2.0	10.7	10.9	210-215	1.5	Not purified further	
<i>p</i> -Dichlorobenzene	160-164	3.0	11.0	10.94	176-182	1.5	11.2	11.3
Toluene	108-122	1.0	(mixture of <i>o</i> and <i>p</i> -isomers)					
( <i>p</i> -Isomer)	122	1.0	13.6	13.6				

washed two or three times with cold water; two washes were generally sufficient to remove the aluminum ions. After the removal of the solvent under reduced pressure, the esters of the mono- and the di-substituted acids were distilled under reduced pressure, preferably at one to five millimeters. The esters were hydrolyzed by refluxing with an excess of concentrated hydrochloric acid, for six to twelve hours, after which the acids were recovered by filtration of the cooled solutions. The benzene derivative, because of its water solubility, required evaporation of the mixture. The yields of the hydrolyses were essentially quantitative.

The relative amounts of the mono- and the di-substituted products may be controlled readily by varying the duration of the refluxing period and the composition of the reaction mixture. Generally speaking, a reaction period of three to eight hours suffices to produce very good yields of the mono-substituted derivatives which are the primary reaction products. The yields in such cases range upward of 70% of the theoretical. If the reaction period is extended to thirty-six or forty hours, substantial yields of the di-substituted derivatives are obtained (frequently 30% or better). The composition of the reaction mixture in respect to the molecular ratios of the hydrocarbon, phosphorus trichloride and aluminum chloride is of importance, particularly in the longer reaction periods. Generally, the aluminum chloride proportions may be varied over a rather wide range, with mole ratios between 0.25 and 1.0 being most satisfactory. The use of less aluminum chloride leads to severely reduced yields and tends to promote the di-substitution in long duration experiments. The use of greater than molar amounts of aluminum chloride appears to suppress the di-substitution to some extent, but appears to show no advantages over the use of short reaction periods to suppress di-substitution. The relative amount of phosphorus trichloride is also a controlling factor, with mole ratios of three to four giving the most satisfactory results in the preparation of mono-substituted derivatives by the short-reflux procedure.

The distillation residues, after the removal of the esters, range from negligible amounts to approximately 20% of crude di-substituted acids, which resulted from partial hydrolysis of the esters in the course of handling.

The properties of the derivatives of benzene, toluene, chlorobenzene, *o*-dichlorobenzene and *p*-dichlorobenzene are given in the following table. Commercial trichlorobenzene (a mixture of the 1,2,3- and 1,2,4-isomers) failed to yield a detectable amount of a phosphorus derivative even after a seventy-two hour reaction period.

The optimum conditions for the synthesis of the mono-

or the di-substituted derivatives may be illustrated by the following data on the derivatives of benzene. With a three-hour refluxing period, the mixture of one mole of benzene, three moles of phosphorus trichloride and one mole of aluminum chloride gave 80.4% of diethyl benzenephosphonate with negligible amounts of the di-substituted product. With a forty-hour refluxing period and the use of six-tenths of a mole of aluminum chloride, there were obtained 58.9% of diethyl benzenephosphonate and 30.1% mono-ethyl bis-benzenephosphinate, with 10% of crude bis-substituted acid remaining after the distillation of the esters, thus giving 99% utilization of the benzene used.

The relatively poorly reactive *o*-dichlorobenzene, under the optimum conditions, and the use of a three-day refluxing period yielded but 36.5% of the mono-substituted derivative and but 2% of the di-substituted product. The even less reactive *p*-dichlorobenzene gave only 3% of the mono-substituted derivative after a thirty-six hour period of refluxing.

Hydrolysis of the esters of benzene and chlorobenzene derivatives yielded the corresponding acids, the melting points of which agreed with the known values for these compounds. Diethyl *p*-toluenephosphonate, after purification by careful fractionation, also gave the known *p*-toluenephosphonic acid; the *ortho*-isomer, however, could not be obtained in a satisfactory degree of purity and was contaminated with traces of the *para*-isomer. The complex isomer mixture of the bis-toluene derivatives could not be resolved by fractional distillation. Hydrolysis of diethyl 3,4-dichlorobenzenephosphonate gave the 3,4-dichlorobenzenephosphonic acid, which was a very hygroscopic solid, which melted indefinitely at approximately 153°; its physical properties prevented a satisfactory analysis. It readily forms an acid sodium salt which decomposes at approximately 260°. Hydrolysis of diethyl 2,5-dichlorobenzenephosphonate gave the 2,5-dichlorobenzenephosphonic acid, which was isolated as the monohydrate, m. p. 194-197° (from dilute alcohol); the latter was found to contain 12.75% phosphorus (theoretical, 12.7% P).

### Summary

The Michaelis modification of the Friedel-Crafts reaction has been greatly improved in respect to the ease of operation and the yield of useful products. The application of the new procedure to benzene, toluene, chlorobenzene and *o*- and *p*-dichlorobenzenes is described.

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